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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,366	02/02/2005	Michele Orlando	14503-010US1	1083

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EXAMINER	
WHITE, EVERETT NMN	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
06/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,366	ORLANDO ET AL.	
	Examiner	Art Unit	
	EVERETT WHITE	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-78* is/are pending in the application.

4a) Of the above claim(s) *57-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-56 and 74-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/4/2005, 1/3/2007, 6/25/2007, 9/26/2007, & 4/28/2008 .

DETAILED ACTION

1. Applicant's election without traverse of Group I, Claims 37-56 and 74-78 in the reply filed on March 14, 2008 is acknowledged.

Foreign Priority Claimed

2. This application is a 371 of PCT/EP03/02084 International Filing Date: February 28, 2003 published in German, which claims foreign priority to Germany 10209822.0 under 35 U.S.C. 119(a)-(d). It is noted that PCT/EP03/02084 and Germany 10209822.0 (March 6, 2002) are in German, no translation of the documents into English has been provided.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 37-45, 47, 48, 50, 52, 56 and 74-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Adamson (CA 2233725 A1).

Applicants claim a conjugate of hydroxyalkylstarch and a low molecular weight substance, characterized in that the binding interaction between the hydroxyalkylstarch molecule and the low molecular weight substance is based on a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group, or a functional group derived from this aldehyde group by chemical reaction, of the hydroxyalkylstarch molecule and (ii) a functional group, which is able to react with this aldehyde group or functional group derived therefrom of the hydroxyalkylstarch molecule, of the low molecular weight substance, where the bonding resulting directly in the coupling reaction can be modified where appropriate by a further reaction to give the abovementioned covalent bonding.

The Adamson CA publication discloses hemoglobin conjugates prepared by reacting hemoglobin with oxidized hydroxyethyl starch, and allowing the resultant conjugate to degrade to a lower molecular weight product, after conjugation. Adamson discloses that the conjugate is then reductively stabilized to form secondary amino bonds between the hemoglobin and the hydroxyethyl starch (see abstract). See lines 1-5 on page 4 of the Adamson publication wherein hydroxyethyl starch is reacted with extracellular hemoglobin, so that the hemoglobin, through primary amine groups of the globin chains reacting with the aldehyde groups of the oxidized starch, covalently binds to the starch through Schiff base linkages. See line 2 on page 8 of the Adamson publication wherein the hydroxyethyl starch starting material used has a molecular weight of from about 70 to about 1000 kDa, which anticipates the molecular weight of the hydroxyethyl starch recited in instant Claims 43 and 44. At line 10 of page 8, Adamson discloses that the degree of substitution of the hydroxyethyl groups ranges from about 0.5 to 0.7, which anticipates the degree of substitution of the hydroxyalkyl starch molecule recited in instant Claim 45. This description of the Adamson publication anticipates the instantly claimed conjugate of hydroxyalkylstarch and a low molecular weight substance.

5. Claims 37-45, 47-56 and 74-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Harboe et al (EP 331471 A, already of record).

Applicants claim a conjugate of hydroxyalkylstarch and a low molecular weight substance, characterized in that the binding interaction between the hydroxyalkylstarch molecule and the low molecular weight substance is based on a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group, or a functional group derived from this aldehyde group by chemical reaction, of the hydroxyalkylstarch molecule and (ii) a functional group, which is able to react with this aldehyde group or functional group derived therefrom of the hydroxyalkylstarch molecule, of the low molecular weight substance, where the bonding resulting directly in

the coupling reaction can be modified where appropriate by a further reaction to give the abovementioned covalent bonding.

The Harboe et al publication discloses anti-inflammatory prodrugs of formula PS-O-A-(CH_2)n-B-D, where PS-OH may be selected as hydroxyethyl starch with a molecular wt. (Mw) of 40,000-5,000,000; A is CO or a direct bond; n is 0-14; B = O, CO, NR or a direct bond; R = H or lower alkyl; D = R1CO or R2O; R1COOH and R2OH = antiinflammatory agents (see the Derwent Abstract), which anticipate the instantly claimed conjugate of hydroxyalkylstarch and low molecular weight substance. The abstract discloses that the anti-inflammatory prodrugs of the Harboe et al publication are used for treating rheumatism, arthritis, gout, and ulcerative colitis, which anticipate the instantly claimed conjugate as a component of a pharmaceutical composition as claimed in instant Claim 56. A list of drugs that can be used in the formula disclosed in the Harboe et al publication are disclosed on pages 6-8 of the Harboe et al publication, which anticipate some of the drugs recited in instant Claims 49, 51, 53 and 55.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 37-45, 47-56 and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adamson (CA 2233725 A1) or Harboe et al (EP 331471 A) or Berger et al (EP 019403 A2) in view of Weidler et al (US Patent No. 5,502,043).

Applicants claim a conjugate of hydroxyalkylstarch and a low molecular weight substance, characterized in that the binding interaction between the hydroxyalkylstarch molecule and the low molecular weight substance is based on a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group, or a functional group derived from this aldehyde group by chemical reaction, of the hydroxyalkylstarch molecule and (ii) a functional group, which is able to react with this aldehyde group or functional group derived therefrom of the hydroxyalkylstarch molecule, of the low molecular weight substance, where the bonding resulting directly in the coupling reaction can be modified where appropriate by a further reaction to give the abovementioned covalent bonding.

The Adamson CA publication discloses hemoglobin conjugates prepared by reacting hemoglobin with oxidized hydroxyethyl starch, and allowing the resultant conjugate to degrade to a lower molecular weight product, after conjugation. Adamson discloses that the conjugate is then reductively stabilized to form secondary amino bonds between the hemoglobin and the hydroxyethyl starch (see abstract). See lines 1-5 on page 4 of the Adamson publication wherein hydroxyethyl starch is reacted with extracellular hemoglobin, so that the hemoglobin, through primary amine groups of the globin chains reacting with the aldehyde groups of the oxidized starch, covalently binds to the starch through Schiff base linkages. See line 2 on page 8 of the Adamson publication wherein the hydroxyethyl starch starting material used has a molecular

weight of from about 70 to about 1000 kDa, which embraces the molecular weight of the hydroxyethyl starch recited in instant Claims 43 and 44. At line 10 of page 8, Adamson discloses that the degree of substitution of the hydroxyethyl groups ranges from about 0.5 to 0.7, which embraces the degree of substitution of the hydroxyalkyl starch molecule recited in instant Claim 45. This description of the Adamson publication embraces the instantly claimed conjugate of hydroxyalkylstarch and a low molecular weight substance.

The Harboe et al publication discloses anti-inflammatory prodrugs of formula PS-O-A-(CH_2)n-B-D, where PS-OH may be selected as hydroxyethyl starch with a molecular wt. (Mw) of 40,000-5,000,000; A is CO or a direct bond; n is 0-14; B = O, CO, NR or a direct bond; R = H or lower alkyl; D = R1CO or R2O; R1COOH and R2OH = antiinflammatory agents (see the Derwent Abstract), which anticipate the instantly claimed conjugate of hydroxyalkylstarch and low molecular weight substance. The abstract discloses that the anti-inflammatory prodrugs of the Harboe et al publication are used for treating rheumatism, arthritis, gout, and ulcerative colitis, which embrace the instantly claimed conjugate as a component of a pharmaceutical composition as claimed in instant Claim 56. A list of drugs that can be used in the formula disclosed in the Harboe et al publication are disclosed on pages 6-8 of the Harboe et al publication, which embrace some of the drugs recited in instant Claims 49, 51, 53 and 55.

The Berger et al patent discloses a hydroxyalkyl-starch drug which is used in a composition for controlled release administration of biologically active compounds to animals. Berger et al discloses that bonding of active compounds to the hydroxyalkyl starch can be a direct reaction. Berger et al discloses that if the active component has a carboxylic acid functional group, it can react directly or indirectly with a hydroxyl group on the hydroxyalkyl starch to form an ester or the active compound can be bound to the hydroxyalkyl starch through a derivative (see page 5, last paragraph). See Scheme I to Scheme III on page 6 of the Berger et al patent for examples of how the active compound may be bonded to the hydroxyalkyl starch polymer which embraces the description of the bonding of the hydroxyalkylstarch to the low molecular weight substance of the instant claims.

The conjugate of the instantly claimed invention differs from the conjugates of the Adamson, Harboe et al and Berger et al publications by claiming that the hydroxyalkylstarch molecule has a ratio of C_2 to C_6 substitution of from 8 to 12.

However, the Weidler et al patent, which discloses the use of hydroxyethyl starch for improvement of microcirculation, shows that the C_2 / C_6 ratio of a hydroxyalkyl starch which covers the 8 to 12 claimed range is known in the art. See the abstract of the Weidler et al patent wherein the C_2 / C_6 ratio of hydroxyethyl starch is disclosed to range from 8 to 20.

One of ordinary skill in this art would be motivated to combine the teaching of the Adamson, Harboe et al and Berger et al publications with the teaching of the Weidler et a patent since each of the references discloses therapeutic applications for hydroxyalkyl starches.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute hydroxyalkyl starches of the Adamson, Harboe et al and Berger et al publications with a hydroxyalkyl starch having a C_2 / C_6 ratio of 8 to 12 in view of the recognition in the art, as evidenced by the Weidler et al patent, that hydroxyalkyl starch is an effective compound for various therapeutic applications.

Summary

8. Claims 37-56 and 74-78 are rejected; Claims 57-73 are withdrawn from consideration as being directed to non-elected inventions.

Examiner's Telephone Number, Fax Number, and Other Information

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Everett White whose telephone number is 571-272-0660. The examiner can normally be reached on 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Everett White/
Examiner, Art Unit 1623

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623